

(19)



Europäisches Patentamt

European Patent Office

Office européen des brevets



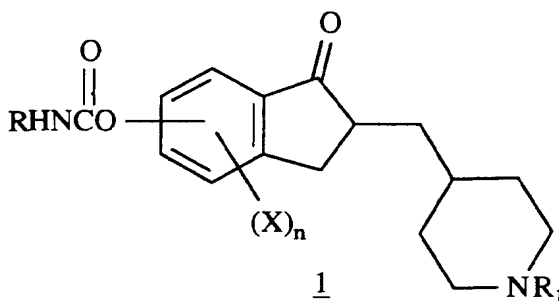
(11) Publication number:

0 535 496 A1

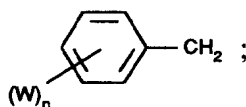
(12)

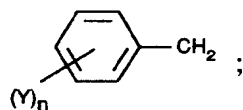
EUROPEAN PATENT APPLICATION(21) Application number: **92116117.0**(51) Int. Cl.⁵: **C07D 211/32, A61K 31/445**(22) Date of filing: **21.09.92**(30) Priority: **25.09.91 US 765279**(43) Date of publication of application:
07.04.93 Bulletin 93/14(84) Designated Contracting States:
**AT BE CH DE DK ES FR GB GR IT LI LU MC
NL PT SE**(71) Applicant: **HOECHST-ROUSSEL
PHARMACEUTICALS INCORPORATED
P.O. Box 2500, Route 202-206
Somerville, NJ 08876-1258(US)**(72) Inventor: **Kosley, Raymond W., Jr.****659 Cedarbrook Road
Bridgewater, N.J. 08876(US)**Inventor: **Spahl, Bettina****518 Village Drive
Edison, NJ 08817(US)**Inventor: **Effland, Richard Charles****544 Rolling Hills Road
Bridgewater, N.J. 08876(US)**(74) Representative: **Becker, Heinrich Karl
Engelbert, Dr. et al
HOECHST AKTIENGESELLSCHAFT Zentrale
Patentabteilung P.O. Box 80 03 20
W-6230 Frankfurt am Main 80 (DE)**(54) **(1-Indanon-2-yl)methylpiperidines, intermediates and a process for their preparation and their use as medicaments.**

(57) The present invention relates to (1-indanon-2-yl)methylpiperidines of the formula



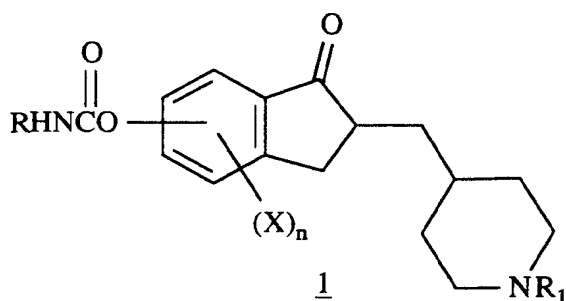
wherein R is hydrogen, loweralkyl, or a group of the formula

R₁ is hydrogen or a group of the formula**EP 0 535 496 A1**

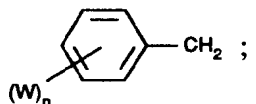


W, X, and Y are hydrogen, loweralkyl, loweralkoxy, halogen, nitro, or trifluoromethyl; n is 1 or 2; the optical isomers thereof, or the pharmaceutically acceptable acid addition salts thereof, which are useful in relieving memory dysfunction, alone or in combination with inert adjuvants, and are thus indicated in the treatment of Alzheimer's disease.

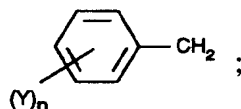
The present invention relates to [[(aminocarbonyloxy)-1-indanon]-2-yl]methylpiperidines of formula 1



wherein R is hydrogen, lower alkyl, or a group of the formula

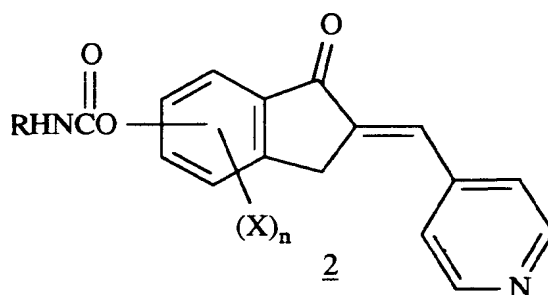


R₁ is hydrogen or a group of the formula

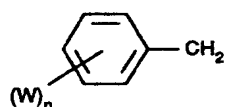


W, X, and Y are hydrogen, loweralkyl, loweralkoxy, halogen, nitro, or trifluoromethyl; n is 1 or 2; the optical isomers thereof; or the pharmaceutically acceptable acid addition salts thereof, which are useful in relieving memory dysfunction, alone or in combination with inert adjuvants, and are thus indicated in the treatment of Alzheimer's disease.

The present invention also relates to 6-(aminocarbonyloxy)-2-[(pyridin-4-yl)methyleneyl]-1-indanones of formula 2



wherein R is hydrogen, lower alkyl, or a group of the formula



wherein W and X are hydrogen, loweralkyl, loweralkoxy, halogen, nitro, or trifluoromethyl; the optical and geometrical isomers thereof; or pyridine N-oxides thereof, which are useful as intermediates for the synthesis of the present [[(aminocarbonyloxy)-1-indanon]-2-yl]methylpiperidines.

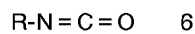
As used throughout the specification and appended claims, the term "alkyl" refers to a straight or branched chain hydrocarbon radical containing no unsaturation and having 1 to 8 carbon atoms. Examples of alkyl groups are methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 1-pentyl, 3-hexyl, 4-heptyl, 2-octyl and the like. The term "alkoxy" refers to a monovalent substituent which consists of an alkyl group linked through an ether oxygen having its free valence bond from the ether oxygen. Examples of alkoxy groups are methoxy, ethoxy, propoxy, 1-butoxy, 1-pentoxy, 3-hexoxy, 4-heptoxy, 2-octoxy and the like. The term "alkanoic acid" refers to a compound formed by combination of a carboxyl group with a hydrogen atom or alkyl group. Examples of alkanoic acids are formic acid, acetic acid, propanoic acid, 2,2-dimethylacetic acid, hexanoic acid, octanoic acid and the like. The term "halogen" refers to a member of the family fluorine, chlorine, bromine, or iodine. The term "lower" as applied to any of the aforementioned groups refers to a group having a carbon skeleton containing up to and including 6 carbon atoms.

The compounds of the present invention which lack an element of symmetry exist as optical antipodes and as the racemic forms thereof. The optical antipodes may be prepared from the corresponding racemic forms by standard optical resolution techniques, involving, for example, the separation of diastereomeric salts of those instant compounds characterized by the presence of a basic group and an optically active acid, or by synthesis from optically active precursors.

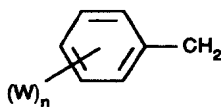
The intermediate 2-[(pyridin-4-yl)methylene]-1-indanones of the present invention exist as geometric isomers in which the pyridinyl group is on the same side or the opposite side of the plane of the carbon-to-carbon bond of the methylene function as the carbonyl bearing moiety of the indanone system. In the trans-isomer the pyridinyl group is on the opposite side of the plane containing the carbon-to-carbon double bond, which is perpendicular to the plane of the page, as the carbonyl moiety; in the cis-isomer the pyridinyl group is on the same side.

The 4-[[6-(aminocarbonyloxy)-1-indanon]-2-yl]methylpiperidines of the present invention are prepared by processes illustrated in the Reaction Scheme.

To gain entry into this system, i.e., to prepare an aminocarbonyloxyindanonylmethylpiperidine 1, a hydroxy-2-[(pyridin-4-yl)methyleneyl]-1-indanone 3, which is described in European Patent Application 0 296 560, published December 28, 1988, is condensed with isocyanic acid or an isocyanate of formula 6



wherein R is hydrogen, loweralkyl, or a group of the formula



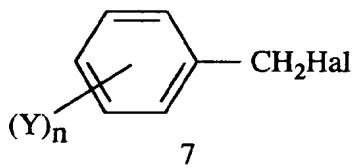
wherein W and n are as hereinbefore described to provide a carbamoyl-2-[(pyridin-4-yl)methyleneyl]-1-indanone 2, which is reduced to a [(carbamoyl)-1-indanon]-2-yl methylpiperidine 4 and, in turn, benzylated to a benzyl[(carbamoyl)-1-indanon]-2-yl methylpiperidine 1. The condensation of a carbinol 3 with an isocyanate 6 is performed in a halocarbon solvent with dichloromethane or trichloromethane, trichloromethane being preferred, in the presence of a base, for example, a tertiary amine such as a trialkylamine selected from the group consisting of trimethylamine, triethylamine, and tri-1- or 2-propylamine at an elevated reaction temperature within the range of about 60° to 120° C, in an enclosed system, a reaction bomb, if necessary. A reaction temperature of about 87°-95° C is preferred.

To prepare a carbamate 2 wherein R is hydrogen, i.e., an N-unsubstituted (aminocarbonyloxy)-2-[(pyridin-4-yl)methyleneyl]-1-indanone 2, a hydroxyindanone 3 may be treated with cyanic acid, generated by and under conditions well-known in the art.

The reduction of a carbamoyl-2[(pyridin-4-yl)methyleneyl]-1-indanone 2 is accomplished by contacting a methyleneylpyridine 2 with hydrogen over a hydrogenation catalyst such as platinum, platinum oxide, palladium, rhodium, or ruthenium, as such, or supported on a material such as carbon, calcium carbonate, or barium carbonate in an alkanoic acid. Included among alkanoic acids are acetic acid and propionic acid. The preferred hydrogenation system consists of platinum oxide and acetic acid. While the pressure and the

temperature at which the hydrogenation is conducted are not narrowly critical, it is preferred to conduct the reduction at a hydrogen pressure of from about 1 to about 20 pounds per square inch (psi) and at a temperature from about ambient temperature to about 60° C. A hydrogen pressure of about 20 psi and a reaction temperature of about ambient temperature are preferred.

The benzylation of a (indanon-2-yl)-methylpiperidine 4 is achieved by following conventional methods involving contacting a piperidine 4 with a benzyl halide of formula 7



wherein Hal is chloro or bromo and Y and n are as hereinbefore described in an alkanone such as, e.g., acetone or 3-butanone in the presence of an acid acceptor such as, e.g., lithium carbonate, potassium carbonate, or sodium carbonate at an alkylation temperature of about ambient temperature. Benzyl bromides and potassium carbonate are the preferred halides and acid acceptor.

Alternatively, a carbamoylindanonylmethylpiperidine 1 is prepared by condensing a [[hydroxy-1-indanon]-2-yl]methylpiperidine 5, which is described in European Patent Application 0 256 506, published December 28, 1988, with isocyanic acid or an isocyanate 6 in an ethereal solvent in the presence of an acid acceptor at a reaction temperature between about 0° C to about ambient temperature. Among ethereal solvents there may be mentioned diethyl ether, 2-methoxyethyl ether, tetrahydrofuran, or dioxane. Among acid acceptors, there may be mentioned lithium carbonate, potassium carbonate, or sodium carbonate. Tetrahydrofuran and potassium carbonate are the preferred solvent and acid acceptor.

The [1-indanon-2-yl]methylpiperidines of the present invention are useful as agents for the relief of memory dysfunction, particularly dysfunctions associated with decreased cholinergic activity such as those found in Alzheimer's disease. Relief of memory dysfunction activity of the instant compounds is indicated by inhibition of acetyl cholinesterase activity in the assay as described below:

Procedure

A. Reagents

1. 0.05 M Phosphate buffer, pH 7.2
 - a) 6.85 g sodium dihydrogen phosphate water/100 ml distilled water
 - b) 13.40 g disodium hydrogen phosphate water/100 ml distilled water
 - c) add a) to b) until pH reaches 7.2
 - d) Dilute 1:10
2. Substrate in buffer
 - a) 198 mg acetylthiocholine chloride (10 mM)
 - b) q.s. to 100 ml with 0.05 M sodium phosphate, pH 7.2 (reagent 1)
3. DTNB in buffer
 - a) 19.8 mg 5,5-dithiobisnitrobenzoic acid (DTNB) (0.5 mM)
 - b) q.s. to 100 ml with 0.05 M sodium phosphate, pH 7.2 (reagent 1)
4. A 2 mM stock solution of the test drug is made up in a suitable solvent and q.sed. to volume with 0.5 mM DTNB (reagent 3). Drugs are serially diluted (1:10) such that the final concentration (in cuvette) is 10⁻⁴ M and screened for activity. If active, IC₅₀ values are determined from the inhibitory activity of subsequent concentrations.

B. Tissue Preparation

Male Wistar rats are decapitated, brains rapidly removed, corpora striata dissected free, weighed and homogenized in 19 volumes (approximately 7 mg protein/ml) of 0.05 M sodium phosphate, pH 7.2 using a Potter-Elvehjem homogenizer. A 25 μ l aliquot of this suspension is added to 1 ml of the vehicle or various concentrations of the test drug and preincubated for 10 minutes at 37° C.

C. Assay

Enzyme activity is measured with the Beckman DU-50 spectrophotometer. This method can be used for IC₅₀ determinations and for measuring kinetic constants.

Instrument Settings

Kinetics Soft-Pac Module #598273

Program #6 Kindata:

Source - Vis

Wavelength - 412 nm

Sipper - none

Cuvettes - 2 ml cuvettes using auto 6-sampler

Blank - 1 for each substrate concentration

Interval time - 15 seconds (15 or 30 seconds for kinetics)

Total time - 5 minutes (5 or 10 minutes for kinetics)

Plot - yes

Span - autoscale

Slope - increasing

Results - yes (gives slope)

Factor - 1

Reagents are added to the blank and sample cuvettes as follows:

Blank:

0.8 ml phosphate buffer/DTNB

0.8 ml buffer/substrate

Control:

0.8 ml phosphate buffer/DTNB/enzyme

0.8 ml phosphate buffer/substrate

Drug:

0.8 ml phosphate buffer/DTNB/drug/enzyme

0.8 ml phosphate buffer/substrate

Blank values are determined for each run to control for non-enzymatic hydrolysis of substrate and these values are automatically subtracted by the kindata program available on Kinetics soft-pac module. This program also calculates the rate of absorbance change for each cuvette.

For IC₅₀ Determinations:

Substrate concentration is 10 mM diluted 1:2 in assay yielding final concentration of 5 mM. DTNB concentration is 0.5 mM final concentration

$$\% \text{ Inhibition} = \frac{\text{slope control} - \text{slope drug}}{\text{slope control}} \times 100$$

IC₅₀ values are calculated from log-probit analysis.

TABLE

Compound	Acetylcholinesterase Inhibiting on IC ₅₀ (mM)
1-benzyl-4-[[6-(methylamino carbonyloxy))-1-indanon]-2-yl] methylpiperidine	1.343
1-benzyl-4-[[6-(butylaminocarbonyl oxy)-1-indanon]-2-yl]methylpiperidine	1.43
1-(3-fluorobenzyl)-4-[[6-(methylamino carbonyloxy)-1-indanon]-2-yl] methylpiperidine	1.508
1-(3-fluorobenzyl)-4-[[6-(benzylamino carbonyloxy)-1-indanon]-2-yl] methylpiperidine	3.17
physostigmine	6.0 x 10 ⁻⁹

Compounds of the invention include

- a. 1-benzyl-4-[[6-(aminocarbonyloxy)-1-indanon]-2-yl]methylpiperidine;
- b. 4-[[6-methylaminocarbonyloxy)-1-indanon]-2-yl]methylpiperidine;
- c. 1-(2-methylbenzyl)-4-[[6-methylaminocarbonyloxy)-1-indanon]-2-yl]methylpiperidine;
- d. 1-(3-methoxybenzyl)-4[[6-methylaminocarbonyloxy)-1-indanon]-2-yl]methylpiperidine;
- e. 1-(4-chlorobenzyl)-4[[6-methylaminocarbonyloxy)-1-indanon]-2-yl]methylpiperidine;
- f. 1-(4-trifluoromethyl)-4[[6-methylaminocarbonyloxy)-1-indanon]-2-yl]methylpiperidine;
- g. 1-(3-fluorobenzyl)-4-[[6-(2-methylbenzylamino-carbonyloxy)-1-indanon]-2-yl]methylpiperidine;
- h. 1-(3-fluorobenzyl)-4-[[6-(3-methoxybenzylaminocarbonyloxy)-1-indanon]-2-yl]methylpiperidine;
- i. 1-(3-fluorobenzyl)-4-[[6-(4-chlorobenzylaminocarbonyloxy)-1-indanon]-2-yl]methylpiperidine;
- j. 1-(3-fluorobenzyl)-4-[[6-(4-trifluoromethylbenzylamino-carbonyloxy)-1-indanon]-2-yl]methylpiperidine;
- k. 1-(3-fluorobenzyl)-4-[[6-(3-methylbenzyl)aminocarbonyloxy)-1-indanon]-2-yl]methylpiperidine;
- l. 1-(3-fluorobenzyl)-4-[[6-(benzylaminocarbonyloxy)-5-methoxy-1-indanon]-2-yl]methylpiperidine;
- m. 1-(3-fluorobenzyl)-4-[[6-(benzylaminocarbonyloxy)-5-chloro-1-indanon]-2-yl]methylpiperidine; and
- n. 1-(3-fluorobenzyl)-4-[[6-(benzylaminocarbonyloxy)-5-trifluoromethyl-1-indanon]-2-yl]methylpiperidine.

Effective amounts of the compounds of the invention may be administered to a subject by any one of various methods, for example, orally as in capsules or tablets, parenterally in the form of sterile solutions or suspensions, and in some cases intravenously in the form of sterile solutions. The basic final products and intermediates, while effective themselves, may be formulated and administered in the form of their pharmaceutically acceptable acid addition salts for purposes of stability, convenience of crystallization, increased solubility and the like.

Preferred pharmaceutically acceptable addition salts include salts of mineral acids, for example, hydrochloric acid, sulfuric acid, nitric acid and the like, salts of monobasic carboxylic acids such as, for example, acetic acid, propionic acid and the like, salts of dibasic carboxylic acids such as, for example, maleic acid, fumaric acid, oxalic acid and the like, and salts of tribasic carboxylic acids such as, for example, carboxysuccinic acid, citric acid and the like.

The active compounds of the present invention may be administered orally, for example, with an inert diluent or with an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the aforesaid compounds may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums and the like. These preparations should contain at least 0.5% of active compound, but may be varied depending upon the particular form and may conveniently be between 4% to about 75% of the weight of the unit. The amount of present compound in such composition is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present invention are prepared so that an oral dosage unit form contains between 1.0-300 mgs of active compound.

The tablets, pills, capsules, troches and the like may also contain the following ingredients: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, corn starch and the like; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; and a sweetening agent such as sucrose or saccharin or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring may be added. When the dosage unit is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil. Other dosage unit forms may contain other various materials which modify the physical form of the dosage unit, for example, as coatings. Thus tablets or pills may be coated with sugar, shellac, or

other enteric coating agents. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

For the purposes of parenteral therapeutic administration, the active compounds of the invention may be incorporated into a solution or suspension. The preparation should contain at least 0.1% of the aforesaid compound, but may be varied between 0.5 and about 50% of the weight thereof. The amount of active compound in such compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present invention are prepared so that a parenteral dosage unit contains between 0.5 to 100 mgs of the active compound.

The solutions or suspensions may also include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

The following Examples are for illustrative purposes only and are not to be construed as limiting the invention.

EXAMPLE 1

1-Benzyl-4-[[6-methylaminocarbonyloxy)-1-indanon]-2-yl]methylpiperidine

A suspension of 4-[[6-methylaminocarbonyloxy)-1-indanon]-2-yl]methylenepyridine (4.58 g), platinum oxide (0.92 g) and glacial acetic acid (185 ml) was shaken at room temperature at 0-10 psi of hydrogen for 0.5 hr. The pressure was then increased to 20 psi of hydrogen, and the suspension was shaken for 1.25 hr, maintaining the pressure at 20 psi of hydrogen. The suspension was filtered, and the filtrate was concentrated. The residue was dried by azeotroping twice with toluene to provide 4-[[6-methylaminocarbonyloxy)-1-indanon]-2-yl]methylpiperidine.

To 4-[[6-methylaminocarbonyloxy)-1-indanon]-2-yl]methylpiperidine was added milled anhydrous potassium carbonate (12.8 g), 4 angstrom sieve-dried acetone (185 ml) followed by benzyl bromide (1.67 ml), with stirring, under nitrogen. The suspension was stirred at room temperature for 1.25 hr, filtered, and the filtrate was loaded onto a silica gel flash chromatography column (solvent: 4 angstrom sieve-dried dichloromethane). The column was eluted with dry dichloromethane, 2% methanol/dichloromethane, and 4% methanol/dichloromethane. The appropriate fractions were combined and concentrated. The residue crystallized on standing. The crystals were dissolved in dry isopropyl alcohol/ethyl acetate and flash chromatographed on silica gel, eluting with ethyl acetate followed by 2% isopropyl alcohol/ethyl acetate. The appropriate fractions were combined and concentrated to provide 1.52 g (24.9%) of product, mp 140-142 ° C.

ANALYSIS:

Calculated for C ₂₄ H ₂₈ N ₂ O ₃ :	73.44%C	7.19%H	7.14%N
Found:	73.93%C	7.11%H	6.99%N

EXAMPLE 2

1-Benzyl-4-[[6-(butylaminocarbonyloxy)-1-indanon]-2-yl]methyl piperidine

To platinum oxide (2.6 g) and 4-[[6-(butylaminocarbonyloxy)-1-indanon]-2-yl]methylenepyridine (12.4 g), under argon, was added glacial acetic acid (480 ml). The suspension was shaken at 20 psi of hydrogen for 1.5 hr and filtered. The filtrate was added to platinum oxide (1.6 g), under argon. The suspension was shaken at 20 psi of hydrogen for 40 min, filtered, and the filtrate was concentrated. The residue was dried by azeotroping with dry toluene to provide 4-[[6-(butylaminocarbonyloxy)-1-indanon]-2-yl]methylpiperidine, as an oil. To the oil was added anhydrous potassium carbonate (46.2 g) and dry 2-butanone (480 ml). To this mixture was added dropwise a solution of benzyl bromide (3.62 ml) in dry 2-butanone (120 ml). The mixture was stirred for 1 hr at room temperature, filtered, and the filtrate was flash chromatographed on

silica gel, eluting with dry dichloromethane and sequentially, 1%, 2%, 3% methanol/dichloromethane, respectively. The appropriate fractions were combined and concentrated to provide 3.2 g (19.2%) of product. Recrystallization from isopropyl alcohol provided analytically pure product, mp 125-127 °C.

ANALYSIS:			
Calculated for $C_{27}H_{34}N_2O_3$:	74.62%C	7.89%H	6.45%N
Found:	74.60%C	7.80%H	6.41%N

EXAMPLE 3

1-(3-Fluorobenzyl)-4-[[6-(methylaminocarbonyloxy)-1-indanon]-2-yl]methylpiperidine

To a stirred suspension of 1-(3-fluorobenzyl)-4-[[6-hydroxy-1-indanon]-2-yl]methylpiperidine (2.31 g), dry tetrahydrofuran (40 ml), and anhydrous potassium carbonate (1.81 g) was added by syringe methyl isocyanate (0.44 ml), under nitrogen at 0 °C. The mixture was stirred at 0 °C for 15 min, allowed to warm to room temperature, and flash chromatographed on silica gel, eluting with chloroform and 1% (dry) methanol/chloroform. The appropriate fractions were combined and concentrated. The other fractions were combined and chromatographed again, employing the same system. The resulting fractions were combined and concentrated. The residues were combined and dried (60 °, 2mm) to provide 1.95 g (72.6%) of product, mp 143-145 °C.

ANALYSIS:			
Calculated for $C_{24}H_{27}FN_2O_3$:	70.22%C	6.63%H	6.82%N
Found:	70.01%C	6.51%H	6.83%N

EXAMPLE 4

1-(3-Fluorobenzyl)-4-[[6-(benzylaminocarbonyloxy)-1-indanon]-2-yl]-methylpiperidine

To a stirred suspension of 1-(3-fluorobenzyl)-4-[[6-hydroxy-1-indanon]-2-yl]methylpiperidine (2.03 g), anhydrous tetrahydrofuran (35 ml), and anhydrous milled potassium carbonate (1.59 g) was added, benzyl isocyanate (0.81 ml) in an ice-bath, by syringe, under nitrogen. The mixture was stirred for 15 min at 0 °C, allowed to warm to room temperature, and flash chromatographed on silica gel, eluting with chloroform, 1% methanol/chloroform, and 2% methanol/chloroform. The appropriate fractions were combined and concentrated to provide, after drying at 80 ° (1 mm), 2.32 g (98%) of product.

ANALYSIS:			
Calculated for $C_{30}H_{31}FN_2O_3$:	74.05%C	6.42%H	5.76%N
Found:	74.29%C	6.45%H	5.80%N

EXAMPLE 5

trans-6-(Methylaminocarbonyloxy)-2-[(pyridin-4-yl)methyleneyl]-1-indanone

To a stirred solution of 6-hydroxy-2-[(pyridin-4-yl)methyleneyl]-1-indanone (12.7 g) in chloroform (190 ml) and triethylamine (35 ml) was added methyl isocyanate (75 ml). The mixture was stirred at 87-95 °C in a stainless steel bomb for 1 hr, cooled to room temperature, and concentrated. The residue was purified by flash chromatography on silica gel, eluting with chloroform followed by 1% methanol/chloroform. Concentration of the appropriate fractions provided 6.33 g (40.1%) of product. Recrystallization from methanol/chloroform provided analytically pure product, mp 208-210 °C, as an approximately 92/8 mixture of trans- and cis-isomers.

ANALYSIS:Calculated for $C_{17}H_{14}N_2O_3$:

69.38% C

4.79% H

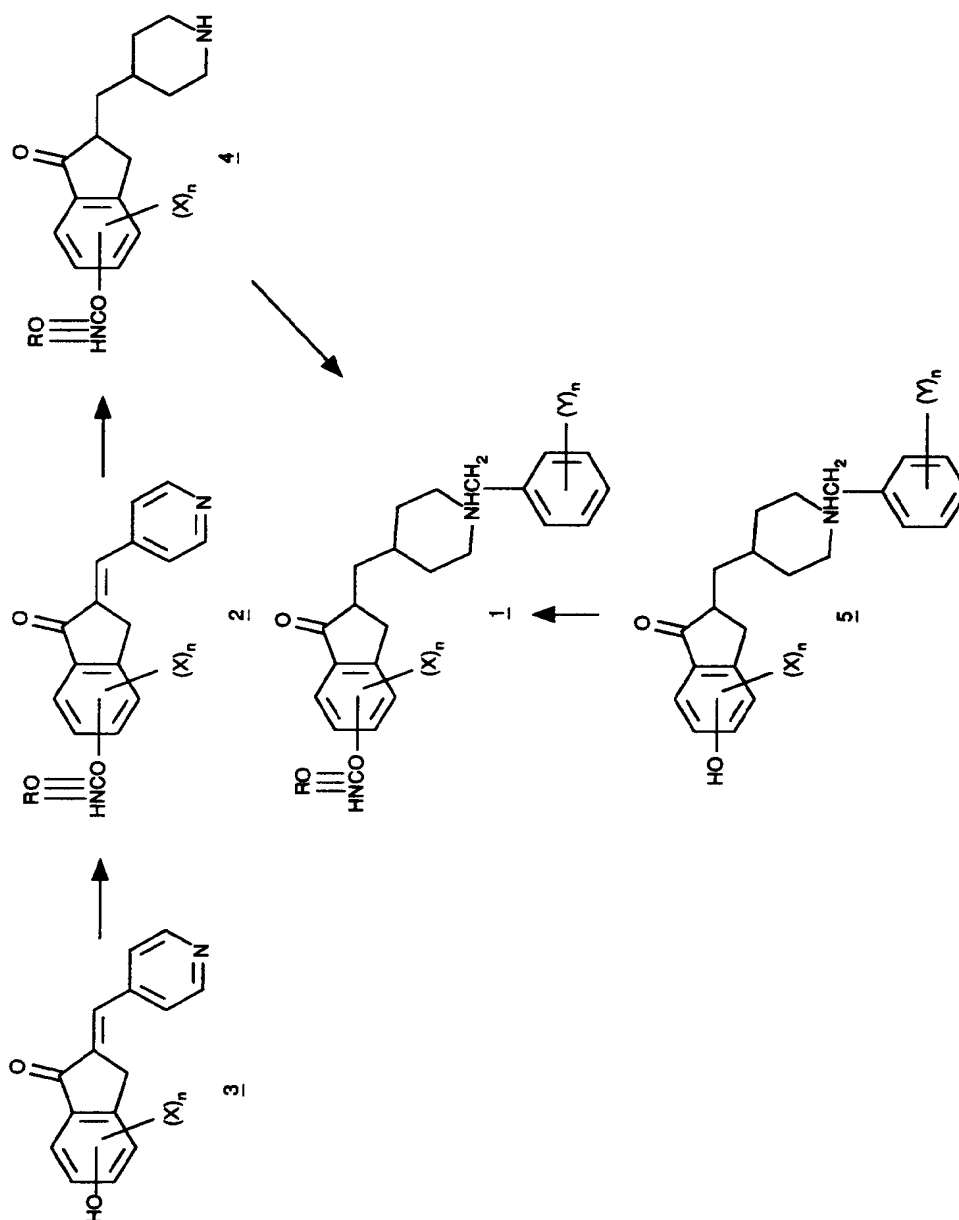
9.52% N

Found:

69.07% C

4.63% H

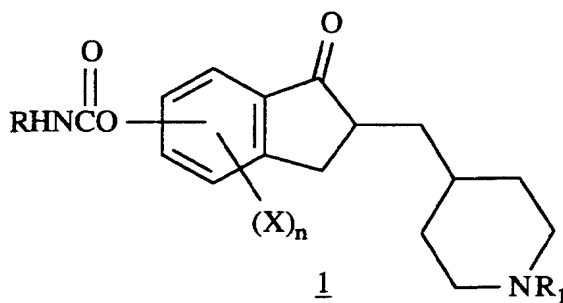
9.40% N

REACTION SCHEME

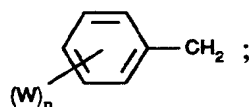
Wherein R, X, Y, and n are as hereinbefore mentioned

Claims

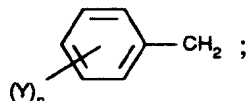
1. A compound of the formula 1



wherein R is hydrogen, loweralkyl, or a group of the formula

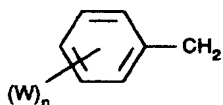


R₁ is hydrogen or a group of the formula

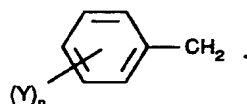


W, X, and Y are hydrogen, loweralkyl, loweralkoxy, halogen, nitro, or trifluoromethyl; n is 1 or 2; the optical isomers thereof; or a pharmaceutically acceptable acid addition salt thereof.

2. A compound as defined in claim 1 wherein R is loweralkyl or a group of the formula



and R₁ is a group of the formula

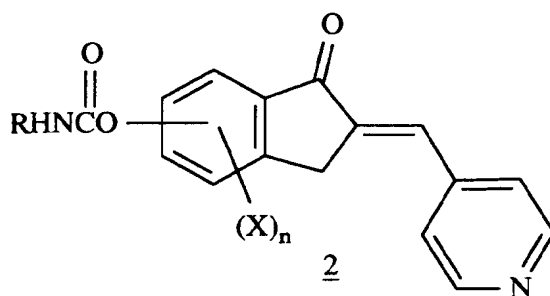


3. A compound as defined in claim 2 wherein W is hydrogen, X is hydrogen, Y is hydrogen or halogen and n is 1.

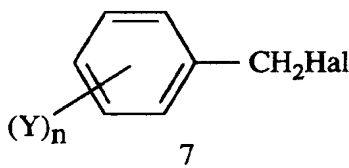
4. A compound as defined in claim 1, which is 1-benzyl-4-[[6-(methylaminocarbonyloxy)-1-indanon]-2-yl]methylpiperidine or a pharmaceutically acceptable acid addition salt thereof.

5. A compound as defined in claim 1, which is 1-benzyl-4-[[6-(butylaminocarbonyloxy)-1-indanon]-2-yl]methylpiperidine or a pharmaceutically acceptable acid addition salt thereof.

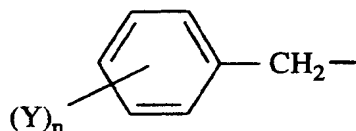
6. A compound as defined in claim 1, which is
1-(3-fluorobenzyl)-4-[[6-(methylaminocarbonyloxy)-1-indanon]-2-yl)methyl]piperidine or a pharmaceuti-
cally acceptable acid addition salt thereof.
7. A compound as defined in claim 1, which is
1-(3-fluorobenzyl)-4-[[6-(benzylaminocarbonyloxy)-1-indanon]-2-yl)methyl]piperidine or a pharmaceuti-
cally acceptable acid addition salt thereof.
8. A pharmaceutical composition which comprises as the active ingredient a compound of the formula 1
as defined in claim 1 and a suitable carrier therefor.
9. Use of a compound for the preparation of a medicament having memory dysfunction relieving activity.
10. A process for the preparation of a compound of the formula 1 as defined in claim 1, which comprises
a) hydrogenating a compound of the formula 2



wherein R, X and n are as defined in claim 1, to form a compound of the formula 1, wherein R₁ is hydrogen, and
b) optionally reacting a compound of the formula 1 as obtained in step a) with a halide of the formula 7



wherein Y and n are as defined in claim 1 and Hal is chloro or bromo, to form a compound of the formula 1, wherein R₁ is a group of the formula



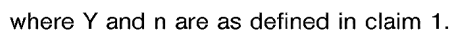
or
c) condensing a compound of the formula 5



20



30



40



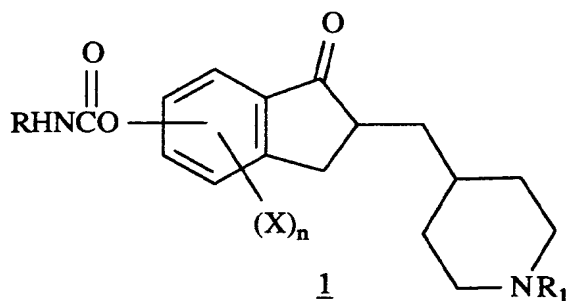
50



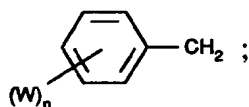
wherein X is hydrogen, loweralkyl, loweralkoxy, halogen, nitro, or trifluoromethyl; n is 1 or 2; the optical and geometrical isomers thereof; or pharmaceutically acceptable salts and pyridine N-oxides thereof.

Claims for the following Contracting State : ES

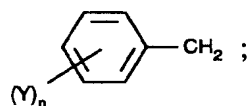
1. A process for the preparation of a compound of the formula 1



wherein R is hydrogen, loweralkyl, or a group of the formula

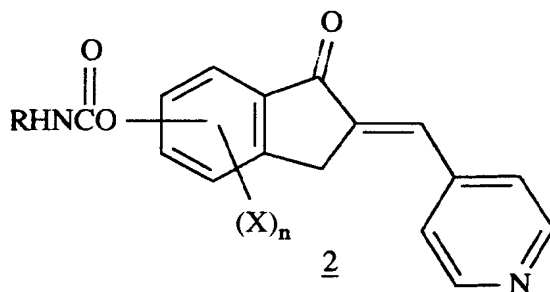


R₁ is hydrogen or a group of the formula



W, X, and Y are hydrogen, loweralkyl, loweralkoxy, halogen, nitro, or trifluoromethyl; n is 1 or 2; the optical isomers thereof; or a pharmaceutically acceptable acid addition salt thereof, which comprises

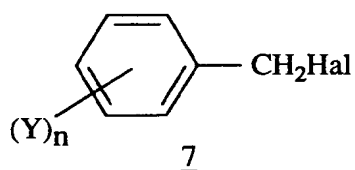
- a) hydrogenating a compound of the formula 2



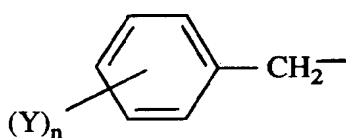
wherein R, X and n are as defined in claim 1, to form a compound of the formula 1, wherein R₁ is hydrogen, and

- b) optionally reacting a compound of the formula 1 as obtained in step a) with a halide of the formula

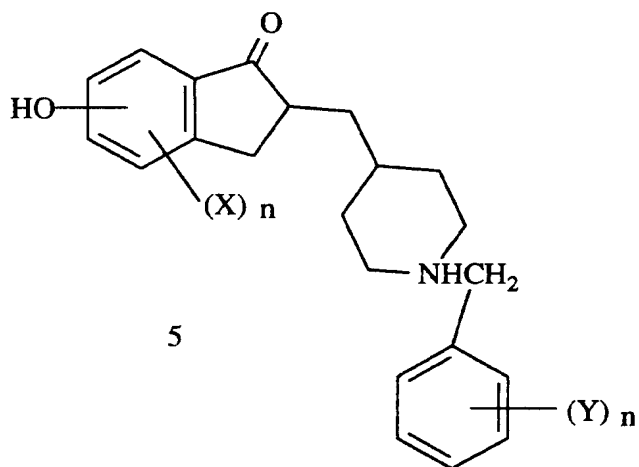
7



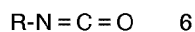
10 wherein Y and n are as defined in claim 1 and Hal is chloro or bromo, to form a compound of the formula 1, wherein R₁ is a group of the formula



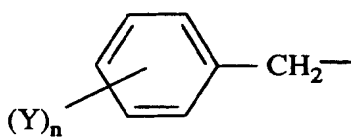
20 or
c) condensing a compound of the formula 5



wherein X, Y and n are as defined in claim 1, with isocyanic acid or an isocyanate of the formula 6

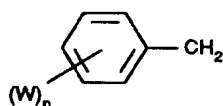


wherein R is as defined in claim 1, to form a compound of the formula 1 wherein R, X and n are as defined in claim 1 and R₁ is a group of the formula

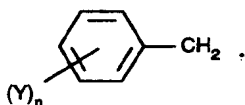


55 where Y and n are as defined in claim 1.

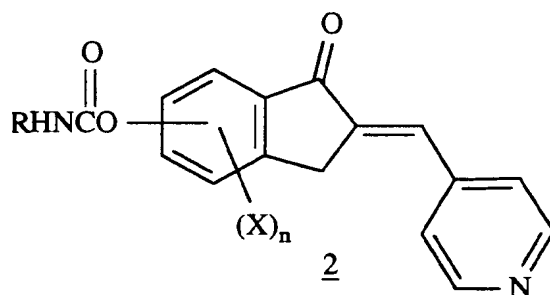
2. A process as defined in claim 1 wherein R is loweralkyl or a group of the formula



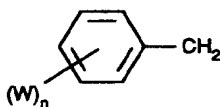
and R_1 is a group of the formula



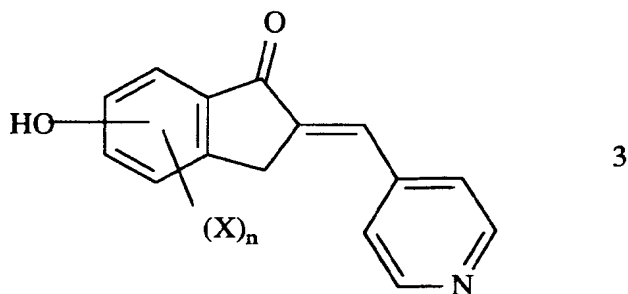
3. A process as defined in claim 2 wherein W is hydrogen, X is hydrogen, Y is hydrogen or halogen and n is 1.
4. A process as defined in claim 1, wherein is
1-benzyl-4-[(6-(methylaminocarbonyloxy)-1-indanon]-2-yl)methylpiperidine or a pharmaceutically acceptable acid addition salt thereof is prepared.
5. A process as defined in claim 1, wherein is
1-benzyl-4-[(6-(butylaminocarbonyloxy)-1-indanon]-2-yl)methylpiperidine or a pharmaceutically acceptable acid addition salt thereof is prepared.
6. A process as defined in claim 1, wherein is
1-(3-fluorobenzyl)-4-[(6-(methylaminocarbonyloxy)-1-indanon]-2-yl)methylpiperidine or a pharmaceutically acceptable acid addition salt thereof is prepared.
7. A process as defined in claim 1, wherein is
1-(3-fluorobenzyl)-4-[(6-(benzylaminocarbonyloxy)-1-indanon]-2-yl)methylpiperidine or a pharmaceutically acceptable acid addition salt thereof is prepared.
8. Use of a compound for the preparation of a medicament having memory dysfunction relieving activity.
9. A process for the preparation of a compound of the formula 2



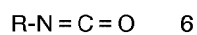
wherein R is hydrogen, loweralkyl, or a group of the formula



wherein X is hydrogen, loweralkyl, loweralkoxy, halogen, nitro, or trifluoromethyl; n is 1 or 2; the optical and geometrical isomers thereof; or pharmaceutically acceptable salts and pyridine N-oxides thereof, which comprises condensing a compound of the formula 3



where X and n are as defined above, with isocyanic acid or an isocyanate of the formula 6



wherein R is as defined above.

25

30

35

40

45

50

55



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 11 6117

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
D,Y	EP-A-0 296 560 (EISAI CO., LTD.) 28 December 1988 * claims 1,3-15 * & Examples ---	1-10	C07D211/32 A61K31/445
Y	PATENT ABSTRACTS OF JAPAN vol. 013, no. 283 (C-612)28 June 1989 & JP-A-1 079 151 (EISAI CO. LTD.) 24 March 1989 * abstract *	1-10	
Y	PATENT ABSTRACTS OF JAPAN vol. 014, no. 435 (C-0760)18 September 1990 & JP-A-2 169 596 (EISAI CO., LTD.) 29 June 1990 * abstract *	1-10	
P,Y	PATENT ABSTRACTS OF JAPAN vol. 016, no. 180 (C-0935)30 April 1992 & JP-A-4 021 670 (EISAI CO., LTD.) 24 January 1992 * abstract *	1-10	TECHNICAL FIELDS SEARCHED (Int. Cl.5)
E	WO-A-9 217 475 (PFIZER INC.) 15 October 1992 * Claims *	1-10	C07D A61K
A	EP-A-0 042 322 (PHARMINDUSTRIE) 23 December 1981 * page 5, line 16 - line 27 *	1-3	
A	EP-A-0 431 945 (MERCK & CO., INC.) 12 June 1991 * claims 1-7; examples 1-3,22,23,31 * -----	1-7	
The present search report has been drawn up for all claims			
Place of search MUNICH		Date of completion of the search 02 DECEMBER 1992	Examiner HERZ C.
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ----- & : member of the same patent family, corresponding document	